

### III. NICOTINE CONTROL

The first argument for the relevance of nicotine to the smoking habit comes from evidence that people smoke to obtain nicotine, and many of them appear to regulate nicotine intake to obtain specific levels of nicotine in their bloodstream. The implication of titration is that smokers have need for nicotine and possess a mechanism in the body which is sensitive to nicotine so enabling them to titrate the dose. Evidence for nicotine need and titration has come from surveys of cigarette preference, studies of inhalation, studies of smoking patterns throughout the day, the titration of individual cigarettes, nicotine preloading studies and a nicotine antagonist experiment.

#### A. Preferred Cigarette Brands

In 1957 the Readers' Digest magazine published a list of the deliveries of nicotine and total particulate matter from cigarette brands in the United States. At that time only one per cent of the cigarettes were filter type and the average cigarette delivered 2.5 mg of nicotine and around 36 mg of particulate matter. After the adverse publicity in the United States from the Surgeon General's report in 1964, and the reports in 1962 and 1971 of the Royal College of Physicians in Britain, the average levels of nicotine, determined by smoking machine analyses, were 1.3 mg. After 1966, American cigarette manufacturers cited tar and nicotine levels in their advertisements and competition began, between the manufacturers, to introduce lower delivery cigarettes onto the market. In 1977 just under half of the United States cigarette industry's budget for advertising and promotion was used to encourage the purchase of these products (US Public Health Service, 1979), and a similar pattern has occurred in the United Kingdom.

It might have been expected that the combination of government publicity and company promotion would have produced an even more remarkable switch in brands to lower nicotine and tar yields in the following ten years, and the sales-weighted average nicotine per cigarette would have decreased at least a further 1.0 mg to 0.3 mg. In fact, cigarettes with a nicotine

1002973426

content of 0.3 mg and correspondingly low levels of particulate matter are not popular, and the sales-weighted average level of nicotine in UK cigarettes has been 1.3 - 1.4 mg per cigarette for the past 8 years, and in the United States it is only approaching 1.1 mg. In Germany there is a similar pattern and the sales-weighted average of nicotine did drop to 0.6 mg but is now around 0.8 mg. The Germany figure may be lower because the Ph of alkaline so increasing absorption (see Section II A). Nicotine-free cigarettes have been a total disaster, even though many people have tried them. Clearly, smokers not only prefer nicotine-containing cigarettes, but most smokers select brands which give a machine smoking delivery of above 1.0 mg of nicotine.

It could be argued that these observations on cigarette preferences do not provide convincing evidence for the importance of nicotine because nicotine usually co-varies with particulate matter in cigarette brands as a consequence of the manufacturing techniques. However, one controlled study has tested cigarettes with independently varied nicotine and tar levels. (Goldfarb, Jarvik and Glick, 1970). Smokers were allowed to smoke as many as they wished of these cigarettes with varying amounts of nicotine and the number of cigarettes that they smoked correlated with nicotine content but not tar content. Ratings of satisfaction and the perceived strength of the cigarette were similarly correlated with nicotine content rather than tar content. Nevertheless, it is interesting that non-nicotine cigarettes were smoked to some extent over the three weeks of the test when there were no other alternatives.

Although low and zero nicotine cigarettes allow the smoker to go through the rituals of lighting, manipulating, and puffing the cigarette as well as inhaling the smoke, the lack of nicotine results in lower consumption. However, it would be fallacious to conclude that flavour from the particular phase of tobacco smoke plays no part in the acceptability of a cigarette. Nevertheless, the inference from these surveys and studies is that nicotine is an essential ingredient of the cigarette for the smoker and this conclusion becomes even clearer when a more complete measure of smoking behaviour, than number of cigarettes smoked, is used.

1002973427

## B. Inhalation

As discussed in Section II, smoke inhalation results in very efficient absorption of nicotine; the large percentage of smokers who inhale provides evidence that the aim of smoking is to obtain nicotine. Epidemiological studies of smoke-related diseases have surveyed self reported inhalation behaviour (Doll and Hill, 1964; Hammond, 1966). Doll and Hill's study showed that 80 - 90 per cent of cigarette smokers reporting inhaling, and Hammond found that 96.4 per cent of smokers, aged between 40 and 49, said that they inhaled to some extent and 85.6 per cent thought that they were moderate to deep inhalers. Todd (1968; 1971) reported similar data with 9 per cent and 8 per cent of smokers believing that they did not inhale at all and 77 per cent saying that they inhaled "a lot" or "a fair amount". The problem with self reported inhalation data is that it may be inaccurate because smokers underestimate the extent to which they inhale (Castleden and Cole, 1973). Therefore the percentage of inhalers is probably higher than these surveys suggest, strengthening the argument that smokers use cigarettes to obtain nicotine.

## C. Smoking Pattern

The hypothesis that smokers attempt to maintain minimum (or above) levels of nicotine is supported by studies of plasma levels of nicotine throughout the day (Russell, Wilson, Patel, Cole and Feyerabend, 1973; Russell, Wilson, Patel, Feyerabend and Cole, 1975). The half-life of nicotine in plasma (see Section II) is about 20 to 30 minutes and habitual smokers consumed 15 to 30 cigarettes per day, ie a cigarette every 30 to 50 minutes (excluding meals and sleep). Russell's studies demonstrated that the mid-morning levels of plasma nicotine were remarkably consistent within subjects across days (small standard error), although the levels for individuals ranged from 5.6 to 83.3 ng/ml. A determination five hours later in the afternoon showed that these levels were either virtually the same or higher which again supports the hypothesis that smokers use cigarettes to obtain nicotine.

1002973428

#### D. Nicotine Titration

In this part I will consider the direct evidence for smokers controlling their nicotine intake either by smoking less intensely with higher delivery cigarettes or smoking more intensely with lower delivery brands. For convenience this section will be sub-divided into cigarette consumption, smoke generation and smoke manipulation, and within each sub-section, the methods of study.

##### 1. Cigarette Consumption

The number smoked is the most obvious way for smokers to control their nicotine intake and it is the easiest to study. However, as we shall see, it is not without its problems. For instance, the number of cigarettes in a pack has a strong influence on consumption. The first studies examined the effects of changing the cigarette brand on consumption.

##### a. Cigarette Switching

The findings of Russell et al (1973; 1975), which strongly hinted that smokers control their nicotine intake were explored further by switching the subjects from their usual brand (1.5 mg average) to both high (3.2 mg) and low (0.3 mg) nicotine cigarettes on different days. The number smoked during the five hours in the middle of the day was recorded. When switched to the high nicotine cigarette, consumption of the group dropped by 37 per cent, from  $10.8 \pm 3.5$  to  $6.7 \pm 1.6$ , and increased, by 17 per cent, from  $10.7 \pm 3.5$  to  $12.5 \pm 3.2$ , when they changed from their usual brand to a low nicotine cigarette (average = mean  $\pm$  standard deviation). The decrease with the high nicotine delivery cigarette was significant but the increase with the low nicotine delivery cigarette was not. However, in terms of nicotine delivery of the latter product, subjects would have needed to smoke five times as many to compensate (an increase from 10.7 to 53.5) if they did not change other aspects of their smoking behaviour in any way.

1002973429

A large scale interview study which looked at the number smoked has given similar findings for switching to lower yield brands. Waingrow and Horn (1968) interviewed a group of 1466 cigarette smokers in 1964 and again in 1966. They found no evidence that smokers, who switched to lower delivery cigarettes, increased their consumption. However, it was again assumed that the smokers did not change their smoking behaviour to obtain more nicotine. Russell (1976) has also pointed out that there may have been self-selection in the sense that only smokers with a low requirement for nicotine switched brands and so could accept the reduced delivery without feeling deprived.

In a shorter term laboratory study, Frith (1971) gave smokers cigarettes with deliveries of 1.02 mg, 1.37 mg and 2.11 mg of nicotine to smoke on single days. The number of cigarettes that were smoked was recorded throughout the day from 9.00 am to 5.00 pm, and the smokers also rated their desire to smoke before and after each one. An inverse relation was found between the number of cigarettes smoked and the nicotine level. Subjects also said that they found the high delivery cigarette more satisfying than the low delivery. Unfortunately, the tar level of the lowest cigarette was half that of the highest (14.6 against 30.8) and so the subjects could easily detect the differences between the products. In a better two hour experiment, smokers were given specially prepared cigarettes which were either of low nicotine delivery (0.2 mg) or high nicotine delivery (2.0 mg) (Jarvik, Popek, Schneider, Baer-Weiss and Gritz, 1978). The tar levels of the cigarettes were identical so that the taste difference was small. Subjects smoked more of the lower delivery than the higher delivery cigarette which gives persuasive support for nicotine regulation.

Better controlled studies have looked at smoking in real life situations. In the first, smokers were given a medium delivery cigarette for the first week, a low to medium cigarette in the second week, and a low cigarette in the third week (Turner, Sillet and Ball, 1974). The subjects compensated by smoking significantly more cigarettes when they switched from the medium to the low-medium cigarettes, but there was little change after the second switch from low-medium to the low delivery product. A longer study (Freedman and Fletcher, 1976)

1002973430

examined the changes in consumption over a 20 month period when smokers were switched from a conventional medium (1.39 mg) nicotine cigarette to a lower medium (1.01 mg) cigarette containing 30 per cent tobacco substitute. The average number of cigarettes smoked remained constant for the first 15 months, but increased slightly in the last 5 months. Although consistent with nicotine regulation, this small but significant increase was surprising in view of the similarity of the nicotine yields of the two cigarettes.

The problems of cigarette consumption experiments were highlighted by long term studies by Adams (1976; 1978) of smokers from the Imperial Tobacco Company Research Division and Head Office which will also be referred to later. Two sets of subjects smoked their own brand for a week, then medium nicotine (1.4 mg) cigarettes for five weeks and then a low-medium nicotine (0.8 mg) cigarettes for four weeks. Two control groups smoked their own brand for a week and then either the low cigarette or low-medium cigarette for the remaining nine weeks. The Research Division subjects increased their weekly consumption markedly when switched to the low nicotine product while the Head Office subjects increased their number only slightly. Adams believes that members of the Head Office smoking panel were less familiar with the experimenters and were inhibited in their demands for more free cigarettes. An equivalent psychological barrier may operate in real life where smokers may choose a lower delivery brand but are reluctant to purchase more cigarettes than they usually do.

A methodologically sophisticated long term study was performed by Finnegan, Larson and Baag (1945) using tobacco leaf with naturally low nicotine content made into a low nicotine (0.34 mg) cigarette or the same leaves sprayed with nicotine and made up into a high nicotine (1.96 mg) cigarette. Thus the pressure drop of the cigarettes and the tar level would be the same and, although the nicotine would give a slightly different taste, it was possible to test the effects on consumption without the subjects being certain about the difference. Subjects were given 400 of the high nicotine product followed by a month on the low nicotine brand and then switched back to 400 of the high nicotine cigarette. The authors claimed that there was no

1002973431

correlation between the number of cigarettes smoked and the nicotine level, a finding which argues against compensation. However, an interesting picture emerged when Russell (1976) examined the distribution of withdrawal symptoms in this study; subjects who did not increase their consumption on the low nicotine cigarette experienced lack of satisfaction, irritability and poorer concentration.

Instead of examining a mixed set of subjects, as in the last study, Schachter (1977) selected an "addicted" group and a "non-addicted" group. The addicted group members had smoked at least 20 cigarettes a day for many years, they smoked regularly throughout the day from morning to night, they inhaled the smoke, they were not trying to stop or cut down at the time of the study, and, if they had tried to abstain, then they had experienced abstinence symptoms. Half the subjects were given low nicotine (0.3 mg) cigarettes for the first week and half were given medium nicotine (1.3 mg) cigarettes for the first week, then they were switched to the other cigarette for the second week. Although the experiment was carried out double blind the cigarettes differed to some extent in tar content. As a group, the addicted smokers smoked 24 per cent more of the low nicotine cigarettes (42.93) than the high nicotine (34.57), while the light smokers used 16 per cent more of the low nicotine (10.19) compared with the high nicotine cigarette (8.81). Schachter reported that three addicted subjects, who only increased consumption by 14.3 per cent compared with 33.6 per cent for the rest, experienced severe abstinence symptoms. Thus the last two studies show that smokers who do not regulate their nicotine intake, suffer deprivation symptoms.

b. Ventilated Holder

Another method of varying smoke delivery to the smoker is to use a normal cigarette but smoked through a ventilated cigarette holder. Two holders producing nicotine dilutions of 23 per cent and 58 per cent were used to study titration (Sutton, Russell, Feyerabend and Sallojee, 1978). Smokers used each holder for a week and kept a diary of their cigarette consumption. Consumption remained constant

1002973432

throughout the study and no titration was seen on this measure. However, as we will see later, compensation was achieved by increasing the amount of smoke inhaled.

c. Partial Cigarettes

A third type of study has examined the number smoked when subjects were only allowed to smoke part of a cigarette for a week. Goldfarb and Jarvik (1972) gave smokers packs of cigarettes which were either cut in half or had a line drawn around them halfway down, and the number of smoked cigarettes was counted. In comparison with smoking their own brand in week 1 (25.5), smoking increased with the lined cigarette (27.2) and the cut cigarette (28.6), but during the fourth week on their own brand smoking was also higher (27.3). These group data give limited support for titration by increasing the number smoked because 12 subjects did increase by an average of five a day on the lined cigarettes and by an average of seven a day on the cut cigarettes. A more extensive study (Russell, Sutton, Feyerabend and Cole, 1978) included a full length medium nicotine (1.08 mg) cigarette, a threequarter length, low-medium nicotine (0.63 mg) cigarette and a half length, low medium nicotine (0.67 mg) cigarette. These cigarettes were smoked in the laboratory on three separate afternoons. The number smoked increased from 13.6 with the full length cigarette, 14.8 with the threequarter length and 17.6 with the half length. Thus there was a clear and significant increase in consumption, in contrast to the rather small changes found by Goldfarb and Jarvik.

d. Nicotine Preload

A fourth approach has been to preload the smokers with nicotine, either by injection or oral doses. The pioneer study of this type, and indeed the first study of titration, was done by Johnston (1942). He injected 20 mg of nicotine intravenously and reported that smokers found the sensation pleasant and did not want to smoke for some time afterwards. No details were given of number consumed. In a follow-up study (Lucchesi, Schuster and Emley, 1967), subjects were given intravenous infusions of nicotine and their cigarette consumption examined. Low

1002973433



doses of nicotine had no effect, but 4 mg per hour very significantly reduced consumption of a cigarette of unspecified delivery by 27 per cent (10 to 7.3). Although significant, this decrease in numbers is small in comparison with the amount of nicotine given, but it must be remembered that nicotine is rapidly metabolised by the liver (see Section II) so that the levels reaching the brain would be much smaller than those infused.

The same problem applies to studies using oral nicotine whether in tablet or chewing gum form so that it is scarcely surprising that a daily dose of five tablets of 1.0 mg of nicotine reduced the number of cigarettes used by only eight per cent although this was a significant decrease (Jarvik, Glick and Nakamura, 1970). Nicotine chewing gum has been prescribed as a stopping-smoking aid; and some success has been claimed. In an experimental study (Russell, Wilson, Feyerabend and Cole, 1976), subjects were given either alkaline gum with nicotine (a high pH increases buccal and gastric absorption; see Section II A.1), or a placebo, both highly spiced so that the subjects could not tell which was which. A plasma nicotine determination showed that nicotine was absorbed from the nicotine gum although blood levels were lower than with smoking. Subjects reduced their smoking on both gums but significantly more so while taking the nicotine gum (37 per cent) than after the non-nicotine gum (31 per cent). Clearly, in spite of a placebo effect, when the subjects thought that they were getting nicotine gum, there was some reduction of consumption.

e. Modified Excretion

A fifth type of study manipulated nicotine body levels by changing urine acidity. If the urine is alkaline then less than one per cent of the nicotine is excreted unchanged in the urine, if it is neutral then seven per cent is excreted and if the urine is acid then 35 per cent is excreted unchanged (Beckett and Triggs, 1967). Presumably an increase in urinary excretion should lower plasma levels of nicotine and so Schachter predicted that increasing acidity should increase smoking. In a test of this prediction (Schachter, Kozlowski and Silverstein, 1977) ascorbic acid (Vitamin C) or glutamic acid

1002973434

hydrochloride was given to smokers to acidify their urine and increase excretion. There were increases in consumption from 23.1 to 26.7 (15.6 per cent) and 28.1 (21.6 per cent) respectively. Once again there was some evidence for control of nicotine intake by changing consumption.

f. Nicotine Antagonists

A complementary study to those on nicotine loading is one using the secondary amine, mecamylamine, which crosses the blood brain barrier and blocks nicotinic synapses in the central nervous system (Stolerman, Goldfarb, Fink and Jarvik, 1973). Smokers were given this drug or pentolinium, a nicotinic blocker which does not enter the brain, and asked to record the number that they smoked of their usual cigarettes (range 1.0 - 1.5 nicotine). Mecamylamine, (7.5 mg, 12.5 mg, 17.5 mg and 22.5 mg) increased cigarette consumption by as much as 30 per cent, presumably smokers smoked more to overcome the partial nicotine blockade in the brain and so obtain the desired effects of nicotine. When the smokers had taken pentolinium there was no change in the number of cigarettes smoked which ruled out any influence of the peripheral effects of nicotine on consumption. This study shows clearly that smokers are using cigarettes to obtain plasma levels of nicotine sufficient to affect the brain.

g. Summary

These studies show that some subjects titrate nicotine by changing the number of cigarettes that they smoke. In studies where abstinence symptoms have been examined, some smokers, who do not compensate, suffer from the effects of nicotine deprivation. However, negative studies may be explained in terms of changes in either puffing or inhalation. Data, that show these factors play a part, come from an experiment by Gritz, Baer-Weiss and Jarvik (1976) in which subjects were given an equal number of full length cigarettes and half length cigarettes to smoke in a week. Urinary nicotine measures showed that subjects were able to obtain considerably more nicotine than expected

1002973435

from the half length cigarettes, and indeed almost as much as from the full cigarette. The authors concluded that "frequency of puff, size of puff or depth of inhalation must have altered on the shorter cigarette to maximise nicotine intake and achieve optimal titration". (P.554).

## 2. Smoke Generation

In the last section, the conclusions on cigarette consumption were related to the nicotine content of the cigarettes. These nicotine levels were calculated on the basis of nicotine deliveries that were obtained from standard smoking machines. The machine smoking determinations enable comparisons of cigarettes, but the smoking machine only produces an approximation of human smoking. The underlying principle of the machine determination of smoke deliveries is that standard analytical procedures are such that the yield is representative of the smoke a cigarette delivers to the smoker if the same smoking parameters are applied. In an innovative series of studies, Creighton and Lewis (1978 a and b) recorded the pattern of smoking in terms of number of puffs, puff interval, puff volume and puff shape. They found that there were marked interindividual differences in smoking pattern and clear, but smaller, intraindividual variations. Therefore it was inevitable that an individual's pattern of generation rarely matched the smoking machine's standard parameters. The consequences of variations in smoking pattern for nicotine deliveries were smaller than those for total particulate matter and carbon monoxide. Nicotine increased markedly with the number of puffs, but there were only small changes for puff interval and puff volume, while puff shape had no effect on nicotine delivery.

The practical consequence of these variations in smoking pattern, in terms of nicotine deliveries, was examined in a complementary study with the puff duplicator (Creighton and Lewis, 1978 a). The divergence of the standard smoking machine yields from the actual values delivered can be seen by comparing the average amount of nicotine that was deposited on the Cambridge filter pad after duplicating the smoking patterns for a medium delivery cigarette having a yield of 1.4 mg of nicotine when analysed on a machine smoking to standard parameters. This was 2.25 mg

1002973436

of nicotine for males and 2.0 mg of nicotine for females. The coefficient of variation for nicotine deliveries between different subjects who smoked the same brand ranged from 24 per cent to 38 per cent with a mean of around 30 per cent. Clearly the machine estimated delivery is a limited index of the nicotine dose entering a smokers mouth, and so other estimates of nicotine delivered to the mouth should be used.

Some of the previous studies of nicotine regulation recorded puff variables as well as numbers of cigarettes consumed. The experiment of Frith (1971) demonstrated that, as well as smoking more cigarettes, smokers took larger puff volumes for some cigarettes than others. Lucchesi et al (1967) found that intravenous nicotine reduced the number of puffs and the subjects discarded their cigarette earlier. A similar study by Kumar (Kumar, Cooke, Lader and Russell, 1977), however, found no changes in puff number, interpuff interval, puff duration or puff volume on a 1.3 mg cigarette after 10 rapid injections of nicotine; either 0.035 mg/kg or 0.07 mg/kg spaced at one minute intervals in order to simulate 10 puffs on a 0.85 mg or a 1.7 mg cigarette. A companion study, with controlled smoking of either a herbal cigarette, a 1.3 mg nicotine cigarette or two 1.3 mg nicotine cigarettes (ie 2.6 mg) did reduce the number of puffs taken from a cigarette in a dose dependent fashion. The major problem with comparing studies of intravenous and inhaled nicotine is that some of the intravenous nicotine is metabolised before reaching the brain and so the dose is lower than that going from lung to brain. This evidence suggests that smokers can control the nicotine intake to their mouth by changing their smoke generation. Direct studies of this behaviour have employed cigarette switching and partial cigarettes.

a. Cigarette Switching

Estimates of nicotine which is drawn into the smokers mouth have been made from analyses of the nicotine deposited in the cigarette filter and the filtration efficiency of the filter tip. One of the first studies on butt nicotine allowed smokers to smoke either a 1.0 mg or 2.1 mg nicotine cigarette while in a driving simulator (Ashton and Watson, 1970). Records were made of puff number and depth of inhalation while the butts were collected. Depth of inhalation was

1002973437

unchanged but puff number was large on the medium delivery cigarette and butt nicotine data showed that about the same amount of nicotine was delivered to the mouth from both cigarettes (1.31 mg from the 1.0 mg nicotine cigarette, a ratio of 1.31, and 1.55 from the 2.1 mg nicotine cigarette, a ratio of 0.74). This study gave clear evidence of titration, by smoking the lower delivery cigarette more intensely and puffing the higher delivery product less intensely. In our own studies (Warburton and Wesnes, 1978) we found similar changes during a vigilance test. Smokers smoked both a low nicotine (0.3 mg) delivery cigarette and a low-medium nicotine (0.7 mg) cigarette more intensely and an estimated 0.68 mg and 1.3 mg of nicotine entered the mouth (ratios of 2.28 and 1.85). When they smoked a 1.64 mg nicotine cigarette, slightly less intensely, they obtained an estimated 1.55 mg of nicotine in the mouth (a puffing intensity ratio of 0.94).

In the longer term study by Turner et al (1974) there were differences in the number of cigarettes smoked between a medium nicotine and a low-medium nicotine product but not between the low-medium and a low brand. There was little difference between the medium and low-medium nicotine cigarettes (puffing intensity ratios of 0.62 and 0.77) but subjects puffed the low delivery cigarette more intensely (a puffing intensity ratio of 1.23). Clearly, the same subjects titrated by changing either the number smoked or the smoke generation in order to obtain their desired nicotine level. In the even longer study by Freedman and Fletcher (1976), in which there were only small changes in the numbers smoked when subjects switched from a 1.39 mg nicotine cigarette to a 1.01 mg product, butt nicotine levels also showed more intense smoking of the lower brand in comparison with the higher delivery cigarette. Puffing intensity ratios of 1.06 and 0.81 were found according to a reanalysis of the data by Rawbone (1976). In another long cross-over study, smokers were studied for four weeks, one week on their usual brand, two weeks on a low delivery cigarette and the final week back on their own cigarette (Forbes, Robinson, Hanley and Colburn, 1976). From butt analysis there was poor evidence of compensation although the subjects were allowed to select their own low delivery product which makes it difficult to draw firm conclusions.

1002973438

As part of their studies using the puff recorder and puff duplicator, Creighton and Lewis (1978 a) studied cigarette switching. Smokers smoked a medium nicotine (1.4 mg) cigarette for one month, a high nicotine (1.8 mg) cigarette for the second month and the medium cigarette again for the third month. The estimated amount of nicotine that was delivered to the mouth of the smoker was assessed from ten laboratory sessions within each month. It was found that the level of nicotine delivered to the mouth stayed constant because subjects reduced their puffing intensity when they switched from medium delivery to high delivery cigarettes and increased their smoking intensity for the opposite switch from high cigarettes back to medium delivery products. However, subjects did not achieve mouth deliveries of 2.0 mg; men obtained 1.7 mg but women only achieved 1.0 mg in spite of their increased smoking intensity. Creighton and Lewis (1978 a) believe that this effect was due to cigarette construction ie, ventilation and longer apparent tip which inhibited smoking to the usual butt length. The clear conclusion was that smokers changed their smoking intensity in the direction of equalising nicotine deliveries. There was no evidence, in this study, that smokers modified the number smoked each day.

In another series of recordings of smoke generation, Adams (1976; 1978) measured puff number, puff volume and puff duration, as well as butt nicotine. He also found that smokers behaved differently on a low-medium nicotine (0.8 mg) cigarette in comparison with a medium delivery (1.4 mg) cigarette; they puffed harder on the lower delivery product and left a shorter butt. Butt nicotine analysis confirmed that more intense smoking resulted in proportionally more nicotine being taken into the mouths of smokers from the low nicotine than from the high nicotine cigarettes. A similar switching experiment (Rawbone, Murphy, Tate and Kane, 1978) studied smokers before and after they switched from their own medium delivery brand (average 1.22 mg of nicotine) to an undefined "low" delivery product. They found that subjects smoked harder on the lower delivery cigarette in comparison with their medium cigarette and compensated quite well (0.83 mg for low-medium against 0.96 mg for the medium delivery brands); as a result of increased puff volume. No increase in consumption was seen.

1002973439

b. Partial Cigarette

In a partial cigarette study, Ashton and her colleagues (Ashton, Stepney and Thompson, 1978) tested subjects with two versions of their usual cigarettes throughout the study; a full length and a two-thirds length, which was calculated for each individual in the following manner. Subjects brought in the butts of their cigarettes, for a 24 hour period, and these were measured. The amount of the cigarette normally smoked was calculated and then a mark was made on the paper at two thirds of this length to indicate the amount of tobacco that they could smoke. The subjects were issued with the same number of marked cigarettes as they had smoked on the previous day and asked not to supplement them. In this way each smoker was deprived to the same degree but not by the same absolute amount. Comparative studies in the laboratory showed that subjects, given the two-thirds cigarettes, increased their puff duration and decreased their puff interval showing more intensive smoking of the reduced cigarette. However, the butt nicotine estimates showed that subjects did not compensate for the reduction sufficiently to obtain their usual amount of nicotine, as smokers had done in the study of Gritz et al (1976). The reason for this difference lies in the part of the cigarette that was smoked in the two studies. It is thought that about 61 per cent of nicotine in the smoke aerosol comes from the half of the cigarette nearer the filter, and only 39 per cent from the other half (Gritz et al, 1976) and so the subjects were not able to compensate sufficiently in the Ashton et al study.

c. Summary

These studies have examined the smoking intensity of low and high delivery brands by estimating the nicotine delivered to the mouth of the smokers from either the amount of nicotine that was deposited in the cigarette butt or puff duplication. The conservative conclusion from this body of data is that there are many different ways of smoking (machine deliveries being merely yields obtained from smoking to a standard set of parameters), and that subjects tend to smoke low delivery cigarettes more intensively and smoke high delivery brands

1002973440

less intensively, even allowing for uncertainties of the filter tip analysis method (Creighton and Lewis, 1978 a).

It should be noted that although the filter tip analysis and puff duplication give an estimate of the amount of nicotine that is delivered to the mouth of the smoker, the value does not represent the effective dose because nicotine is not readily absorbed by the mouth from acidic smoke (see Section II A.1). Cigarette smoke must be inhaled for maximum absorption of nicotine. Of course over 90 per cent of smokers say that they usually inhale to some extent and 77 per cent say that they usually inhale "a lot" or "a fair amount" (Todd, 1972 TRC) so it is likely that a high percentage of the nicotine actually retained in the mouth is made available for absorption by the lungs, but accurate measures of the nicotine titration can only come from first estimating the amount of unwanted nicotine rejected from the mouth before inhalation (the "waste smoke") and then measuring inhalation itself.

### 3. Smoke Manipulation

Smoke manipulation particularly inhalation was apparently the most surprising aspect of the smoking habit for the Spaniards who first saw the American Indians smoking, but it is this manipulation which enables nicotine absorption. One index of manipulation is the amount of carbon monoxide exhaled after a cigarette. Carbon monoxide is absorbed into the bloodstream from the lungs and not in the mouth, so that increased carboxyhaemoglobin occurs only after inhalation. When the residual smoke has been expelled from the lungs, after a cigarette, carbon monoxide exchange from the blood to the lungs will occur so that the level of exhaled end-tidal carbon monoxide provides an index of uptake at the lungs and so enables comparisons of smoke manipulation.

#### a. Cigarette Switching

In a study referred to twice before, switching from smoking medium nicotine (1.4 mg) cigarettes to either high nicotine (3.2 mg) or low nicotine (0.3 mg) cigarettes was compared over a five hour work period by measuring exhaled carbon monoxide (Russell et al, 1973).

1002973441



The problem of interpreting the results was the difference in carbon monoxide yields of the two cigarettes and the fact that the subjects slightly increased consumption of the low delivery and decreased the number of higher delivery cigarettes smoked. Exhaled carbon monoxide decreased for both switches and Russell has argued post hoc that the decrease with the high cigarettes represented less inhalation while the decrease with the low cigarettes was attributable to the lower carbon monoxide yield of that product. Plasma nicotine measures showed clear titration in half of the subjects when switched to the high nicotine cigarette while there was some evidence of titration for the group as a whole when switched to the low nicotine cigarette. When Ashton and Telford (1973) used unspecified high nicotine cigarettes and low nicotine cigarettes but with the same carbon monoxide delivery, the levels of exhaled carbon monoxide were inversely proportional to the nicotine deliveries of the cigarettes giving evidence of titration smoke manipulation.

Strong support for this conclusion was obtained from subjects who switched from a high nicotine (1.7 mg) cigarette with 17.2 mg of carbon monoxide to a low-medium nicotine (0.7 mg) cigarette with only 11.4 mg of carbon monoxide for five weeks (Guillerm and Radziszewski, 1974). Consumption increased slightly by three a day but carbon monoxide levels increased from 5.78 per cent to 7.43 per cent even though the machine estimated delivery of carbon monoxide from the low-medium nicotine cigarette was lower. In contrast, the shorter study of Turner et al (1974) found only slight evidence for compensation by smoke manipulation on the lower delivery brands.

More convincing evidence comes from an eleven week crossover study (Ashton, Stepney and Thompson, 1978) in which smokers switched from their usual medium (1.4 mg) nicotine brand to either high (1.84 mg) nicotine cigarettes ie an increase of 31 per cent in delivery or low-medium (0.6 mg) cigarettes ie a decrease of 57 per cent in delivery. The exhaled carbon monoxide levels showed an increase of only 10 per cent on the high nicotine cigarette, and were only 15 per cent lower on the low-medium cigarette. The plasma nicotine levels showed a similar pattern indicating that considerable post

1002973442

puffing titration had occurred. Urinary nicotine excretion on the high nicotine cigarette gave no support for titration when the machine delivery of 31 per cent higher than the usual brand was matched by urinary nicotine levels 30 per cent higher with the high nicotine cigarette than with the usual brand. However with the low nicotine cigarette, at 43 per cent of the usual cigarette the 24 hour excretion was 94 per cent. Altogether this study gives strong support for nicotine titration by smoke manipulation.

b. Partial Cigarettes

The experiment with half and three-quarter length cigarettes of Russell et al (1978) also included determinations of exhaled carbon monoxide and plasma nicotine. Although smokers used a greater number of the partial cigarettes, there was no evidence that they inhaled more carbon monoxide than would have been expected from the size of the cigarettes and the plasma nicotine was at the expected level as well, suggesting no titration. We will return to this contradictory result in the next sub-section.

c. Ventilated Holder

The results of the study on the ventilated holder (Sutton et al, 1978) which gave no support for titration in terms of the number smoked did provide some evidence for titration by smoke manipulation. A comparison of the observed 33 per cent reduction of carbon monoxide by the more ventilated holder at two days and seven days with the expected reduction of 52 per cent showed partial but significant compensation which was maintained throughout the test week. There seemed to be no compensation with the less ventilated holder which reduced carbon monoxide by 15 per cent. The outcome, in terms of plasma nicotine, was a reduction of only 40 per cent instead of the expected 58 per cent which confirms the effectiveness of smoke manipulation as a titration mechanism. This clear finding contrasted with the study of Russell et al (1978; Russell, 1980) in which partial cigarettes were smoked. Although smokers consumed more cigarettes in this study, their expired carbon monoxide and plasma nicotine levels were the same as those predicted if no titration had occurred. This study implies that smoke concentration is the cue for smoke manipulation because total

1002973443

smoke inhaled increased for smoke diluted by ventilation but not when the smoke concentration was the same as in the partial cigarettes (Russell, 1980).

d. Nicotine Preloading

As part of a series of studies on titration we administered an oral 1.0 mg dose of nicotine to smokers prior to smoking a low-medium nicotine (0.6 mg) cigarette (Wesnes, Pitkethley and Warburton, in preparation). The subjects were not told the true nature of the study and thought they were participating in a study of smoking and the effect of absorption of pure nicotine on hand tremor. Puffing behaviour, butt nicotine and exhaled carbon monoxide were measured. No differences were seen in puff duration and puff interval or the butt nicotine levels for the nicotine and placebo conditions. However, there was a significant reduction of exhaled carbon monoxide after the subjects had received a nicotine tablet indicating reduced smoke inhalation. Clearly the smokers were titrating their nicotine dose by smoke manipulation according to some internal mechanism sensitive to plasma nicotine levels.

e. Summary

Nicotine intake can be controlled by the amount of smoke inhaled as well as by cigarette consumption and by smoke generation. The amount of smoke inhaled depends on a combination of the quantity of waste smoke (the surplus expelled before inhalation) and the degree of inhalation. Rawbone et al (1978) compared exhaled carbon monoxide levels with smoke generation measures and found no correlation. Some smokers puffed relatively little but perhaps wasted little and inhaled the remaining smoke deeply, others puffed hard but perhaps wasted more and inhaled little. Thus, mechanisms are not necessarily interdependent. As far as nicotine absorption is concerned, inhalation is the final control on intake.

1002973444

#### 4. Conclusions

The experiments in this section were designed to investigate to what extent nicotine intake was controlled and the changes in smoking behaviour that enabled control. Taken together the studies show that nicotine intake is titrated to obtain more nicotine from lower delivery cigarettes and less nicotine from higher delivery brands. The methods of titration are number of units smoked, the length of cigarette smoked, the intensity of smoke generation, and the amount of smoke manipulation (waste smoke and inhalation). Unfortunately, most studies have only studied one of these titration mechanisms and found that some subjects do titrate, some titrate partially and some may not titrate at all using that particular method. Indeed it may be possible to titrate completely with some low delivery brands and the plasma nicotine levels in the studies of Russell support this assertion.

Evidence for control over the nicotine dose is important. It argues not only for nicotine being a necessary condition for smoking but also that smokers are trying to obtain a dose which will produce desired or needed pharmacological effects. Before considering the range of these pharmacological effects of nicotine it should be pointed out that the titration evidence suggests low delivery cigarettes will not necessarily be safer because they are oversmoked and tar exposure will increase to medium delivery levels while the carbon monoxide levels can exceed those of high delivery cigarettes (Ashton and Telford, 1973). Lowering deliveries can only be done effectively when we understand more fully the cues and mechanisms that smokers use to adjust their nicotine intake.

1002973445